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(54) Title: BIOPOLYMERS COMPRISING HUMAN IMMUNODEFICIENCY VIRUS TAT

(57) Abstract: This invention relates to the use of oligourea molecules to specifically inhibit protein-nucleic acid interactions. In particular, it provides an oligourea molecule that competes with the Tat molecule for the TAR RNA of HIV-1. Also provided is a method specifically inhibiting protein-nucleic and interactions, and kits.

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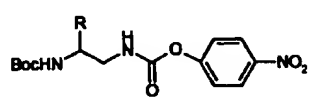
(54) Title: MONOMERS AND OLIGOUREA PEPTIDOMIMETICS AND PROCESS FOR THE PREPA RATION THEREOF



(I)

(57) Abstract

The invention relates to novel protected monomer building blocks of formula (I) wherein R represents a side-chain of a natural or unnatural, common or uncommon amino acid wherein optionally present functional groups are protected, to a process for the preparation of these monomers and to the use thereof for the solid phase synthesis of oligourea peptidomimetics.

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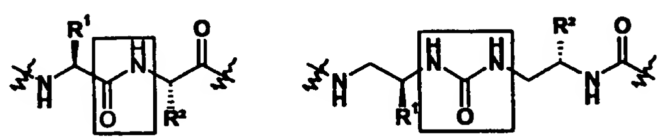
MONOMERS AND OLIGOUREA PEPTIDOMIMETICS AND PROCESS FOR THE PREPA RATION THEREOF

The invention relates to novel protected monomers, the preparation thereof and their use for the preparation of oligourea peptidomimetics.

In recent years, an increasing amount of attention has been focused on the application of the urea moiety as a replacement for the amide bond in peptidomimetics. The resulting *oligourea peptidomimetics* offer several advantages in comparison with natural peptides regarding prospective therapeutic applications. As in other types of peptidomimetics, replacing the amide bond leads to a decrease in degradation by proteolytic enzymes in the gastro-intestinal tract, which opens perspectives for the oral delivery of these compounds.

The backbone in each repeating unit of oligourea peptidomimetics is generally extended by one carbon atom in comparison with the natural amino acid

Figure 1



amide unit in peptides   urea moiety in urea peptidomimetic

This is done for reasons of synthetic accessability and product stability. In addition, the extra carbon atom may also increase the lipophilicity and flexibility of the compounds which makes it easier to pass barriers like the cell wall and the blood–brain barrier. The hydrogen-bond-forming capacity of the urea unit on the other hand might help in rendering the urea compounds more water soluble than the natural peptide. Moreover, an appropriately placed hydrogen-bonding unit may cause additional affinity in interaction with a receptor.

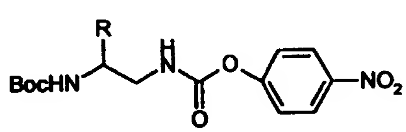
Examples of solid-phase synthesis of oligourea peptidomimetics in the literature have been described by the groups of Burgess and Schultz. (Angew. Chem. Int. Ed. Engl. (1995), 34, 907-909; Angew. Chem. (1995), 107, 975-977; J. Am.Soc. (1997), 119, 1556-1564; Tetrahedron Lett. (1996), 37, 5305-5308, and 5309-5312). Burgess et al. were the first to describe a solid-phase synthesis of oligourea peptidomimetics, employing phthalimide-protected isocyanates as monomers. The phthalimido group, since it has to be removed under relatively harsh conditions (60% $N_2H_4.H_2O$ in DMF), is generally considered a less suitable α-amino protective group.

Schultz et al. have developed an elegant procedure in which azido 4-nitrophenyl carbamate monomers are used for the solid-phase synthesis of oligoureas. In their procedure the final product is cleaved off as a urea instead of the C-terminal carboxylic acid or amide.

The invention relates to a procedure for the synthesis of oligourea peptidomimetics using more usual protective-groups, instead of the phthalimido and azido groups (vide supra) which could be easily implemented on commercial peptide or robot synthesizers. Moreover, the aim of the invention is the preparation of the C-terminal free acids, since a carboxyl terminus is often essential for the biological activity of peptides and peptidomimetics.

It has been found that the objectives of the invention can be achieved by using novel urea monomer building blocks in a solid phase synthesis for the preparation of oligourea peptidomimetics having a free carboxyl terminus.

The novel monomer building blocks are t.butoxycarbonyl (Boc)-protected monomers of the formula (I)



(I)

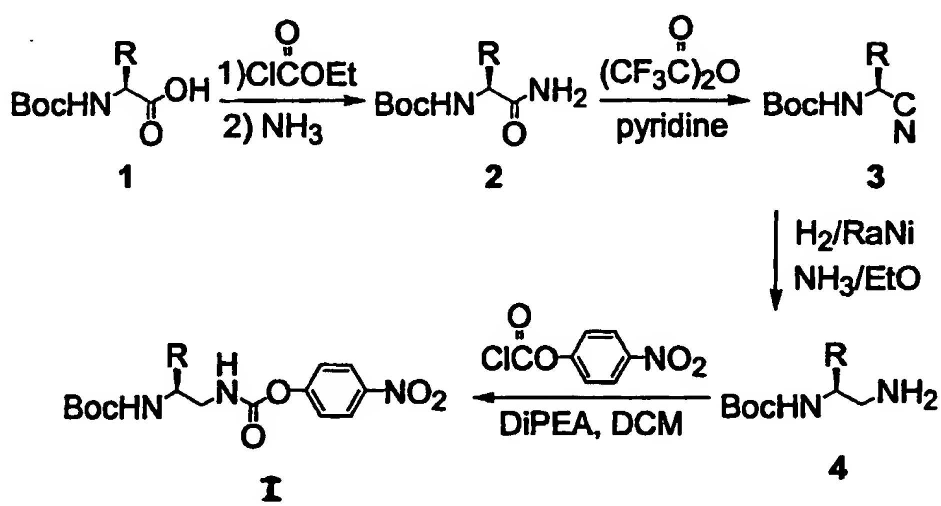
wherein R represents a side-chain of a natural or unnatural, common or uncommon amino acid wherein optionally present functional groups are protected.

Preferred building blocks of the formula (I) are monomers wherein R represents the side-chain of a natural or unnatural amino acid, especially the side-chain of one of the following amino acids: phenylalanine, O-protected tyrosine, leucine, O-protected serine, N-protected lysine or glycine.

These monomers can be prepared and stored as stable, crystalline Boc-protected activated 4-nitrophenyl carbamate derivatives, which are converted in situ into isocyanates when used in the below described solid phase synthesis of oligourea peptidomimetics.

The monomers having formula (I) can be prepared as indicated in Scheme1.

<u>Scheme 1</u>



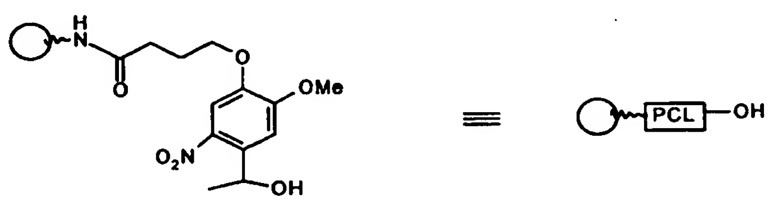
side chains

a Phe: R = CH_2Ph
b Tyr: R = $CH_2(C_6H_4)OBn$
c Leu: R = $CH_2CH(CH_3)_2$
d Ser: R = CH_2OBn
e Lys: R = $(CH_2)_4NHZ$
f Gly: R = H

The preparation of compounds 1-4 of Scheme (1) can be carried out according to processes known per se.
The conversion of amine (4) into an active carbamate (I) with 4-nitrophenyl chloroformate is carried out in the presence of a tertiair amine, such as DiPEA, as a base. This reaction proceeds in high yields.

A further objective of the invention is the solid phase synthesis of a oligourea peptidomimetics having a free carboxyl terminus.

It has been found that this can be achieved by a) coupling a N-protected amino acid to photocleavable linker (PCL) containing resin (5), b) removing the protective group, giving product (6), c) adding a solution of an activated monomer (I), d) removing the protecting group from the N-terminus, e) repeating steps c) and d) n-times giving product (6), n being the number of monomer building blocks, and f) cleaving the oligourea peptidomimetic photolytically from the resin to obtain an (optionally side-chain protected) oligourea peptidomimetic product (8), from which the (optionally side-chain protecting groups and) the N-protecting Boc group can be removed in a manner known per se.



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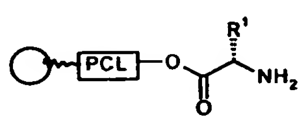

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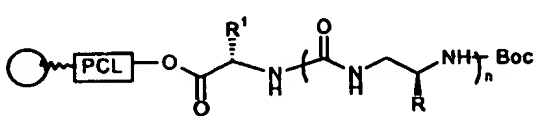

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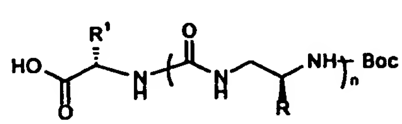


(8)

In these formulae (5) – (8) PCL means photocleavable linker (linked to the resin), R^1 is the side-chain of an amino acid, R has the meaning given above, and n is the number of monomers (which can be the same or different) in the oligourea peptidomimetic.

The use of standard protective group chemistry has the advantage that the urea monomers can be incorporated in a simple manner into peptides and peptidomimetics, even using automated procedures, with minimum adjustments of the protocol and reagents needed for coupling and deprotection.

The invention will now be illustrated by means of the following expamples.

List with abbreviations

Boc = t. butoxycarbonyl	DiPEA= dissopropylethylamine
DCM= dichloormethaan	PCL= photocleavable linker
O= resin	THF=tetrahydrofuran
DMAP= N, N'-4-diaminopyridine	Z= benzyloxycarbonyl
MMP= N-methylpyrrolidone	TEA= triethylamine
DMSO= dimethylsulfoxide	TFA=trifluoroacetyl
Fmoc=9-fluorenylmethoxycarbonyl	Bn=benzyl

General Remarks: Unless stated otherwise, chemicals were obtained from commercial sources and used without further purification. Hydroxyethyl Photolinker Novasyn® TG resin **(5)** was purchased from NovaBiochem, Laûfelfingen, Switzerland. All protected amino acids were purchased from Advanced Chemtech (Belgium). THF, NMP and DCM were purchased from Biosolve, the Netherlands. THF was distilled immediately prior to use from $LiAlH_4$. NMP and DCM were stored on molecular sieves (4 Å). Hexanes had a boiling range of 60–80 °C. DiPEA and TEA were distilled from ninhydrin and KOH. Pyridine was distilled from KOH. Column chromatography was perfomed on Merck Kieselgel 60 (40–63 µm). – NMR: Varian G-300 (300.1 and 75.5 MHz, for ^{1}H and ^{13}C, respectively). For ^{1}H NMR, $CDCl_3$ as solvent, TMS as internal standard; [D_6]DMSO as solvent, $\delta_H = 2.50$. For ^{13}C NMR, $CDCl_3$ $\delta_C = 77.0$;

$[D_6]$DMSO δ_C = 39.5 . – FAB MS: JEOL MS SX/SX 102A four-sector spectrometer coupled with a HP-9000 data system. – Analytical HPLC: Gilson automated HPLC with Unipoint software, equipped with an analytical reversed-phase column (Alltech Adsorbosphere C8, 5µm, 250 × 4.6 mm) and a UV detector operating at 220 nm. Elution was effected using an appropriate gradient from 0.1% TFA in water to 0.085% TFA in acetonitrile/water (95/5, v/v), at a flow rate of 1 mL min^{-1}. – Preparative HPLC: Gilson automated HPLC with Unipoint software, equipped with an preparative reversed-phase column (Alltech Adsorbosphere C8, 10 µm, 250 × 22 mm) and a UV detector operating at 220 nm. Elution was effected using an appropriate gradient from 0.1% TFA in water to 0.085% TFA in acetonitrile/water (95/5, v/v), at a flow rate of 11.5 mL min^{-1}. – UV lamp:Vilber Lourmat TFP-35L UV table. – IR: Bio-RAD FTS-25. – Polarimeter: Jasco P-1010.

Examples

Example 1: Preparation of activated monomers

Activated Monomers (I) (Scheme 1), General Procedure: Raney nickel (50% slurry in water, 3 g) was washed with absolute ethanol (3 ×), and nitrile **3** (Scheme 1) (5.0 mmol) and a saturated solution of NH_3 in ethanol (50 mL) was added. After hydrogenation in a Parr apparatus under 3 bar pressure for 4 h, the reaction mixture was filtered over Celite and the volatiles were removed in vacuo. Subsequently, crude amine **4** (Scheme 1) (5.0 mmol) was dissolved in DCM (15 mL) and DiPEA (0.87 mL, 5.0 mmol) was added. Under a nitrogen atmosphere, the resulting solution was added slowly to a cooled (0 °C; ice bath) solution of *p*-nitrophenylchloroformate (1.1 g, 5.5 mmol) in DCM (10 mL) and stirring was continued for 1 h. The solvent was evaporated in vacuo and the residue was redissolved in EtOAc. The organic layer was washed with 1 N $KHSO_4$ (2 ×) and dried (Na_2SO_4). After the solvent was removed in vacuo, the product was crystallized from EtOAc/hexanes. If the reaction product crystallized from the reaction mixture, the mixture was filtered before work up. The residue was washed with hexanes to give a first yield of product. The filtrate was subjected to work up as described above.

a) Activated Phenylalanine Monomer : The product precipitated during the synthesis. 3.1 g (5.8 mmol, 90% over two steps) white solid was obtained from **3a** (1.60 g, 6.5 mmol); m.p. > 128 °C (decomp.). R_f (2:1 hexanes:EtOAc): 0.38. – $[\alpha]_D^{23}$ = – 11.1 (c = 0.48, dioxane). – ^1H NMR ($CDCl_3$): δ = 1.42 [s, 9 H, $C(CH_3)_3$], 2.80–2.87 (m, 2 H, $CH_2C_6H_5$), 3.26–3.46 (m, 2 H, CH_2NH), 4.04 (m, 1 H, *CH*NH), 4.66 (bs, 1 H, BocNH), 5.76 [bs, 1 H, N*H*C(O)O*p*–$C_6H_4NO_2$], 7.20–7.35 (m, 7 H, C_6H_5 + 2 × *p*-$C_6H_4NO_2$), 8.21–8.25 (m, 2 H, 2 × *p*-$C_6H_4NO_2$) – ^{13}C NMR ($CDCl_3$): δ = 28.3 [$C(CH_3)_3$], 38.9 ($CH_2C_6H_5$), 45.6 (CH_2NH), 51.9 (CHNH), 80.1 [$C(CH_3)_3$], 121.9, 125.1, 126.9, 128.7, 129.1, 136.9, 144.8, 155.9 (C_6H_5 + *p*-$C_6H_4NO_2$), 155.9 [$C(O)OC(CH_3)_3$], 156.2 [*C*(O)], 156.3 [*C*(O)]. – FAB MS: *m/z* = 416.2 $[M + H]^+$. – $C_{21}H_{25}N_3O_6$ (415.45) calcd. C 60.71, H 6.07, N 10.11; found C 60.11, H 6.05, N 9.98.

b) Activated Tyrosine Monomer : The product precipitated during the synthesis. 2.7 g (5.2 mmol, 81% over two steps) white solid was obtained from **3b** (2.27 g, 6.4 mmol); m.p. > 136 °C (decomp.). R_f (2:1 hexanes:EtOAc): 0.36. – $[\alpha]_D^{23}$ = – 5.2 (c = 0.53, dioxane). – ^1H NMR ($CDCl_3$): δ = 1.43 [s,9 H, $C(CH_3)_3$], 2.71–2.86 (m, 2 H, $CH_2C_6H_4O$), 3.21–3.50 (m, 2 H, CH_2NH), 3.99 (bs, 1 H, *CH*NH), 4.66 (bs, 1 H, BocNH), 5.05 (s, 2 H, $CH_2C_6H_5$), 5.81 [bs, 1 H, N*H*C(O)O*p*-$C_6H_4NO_2$], 6.94 (d, *J* = 8.8 Hz, 2 H, $CH_2C_6H_4O$), 7.13 (d, *J* = 8.8 Hz, 2 H, $CH_2C_6H_4O$) 7.27–7.45 (m, 7 H, $OCH_2C_6H_5$ + 2 × *p*-$C_6H_4NO_2$), 8.21–8.26 (m, 2 H, 2 × *p*-$C_6H_4NO_2$). – ^{13}C NMR ($CDCl_3$): δ = 28.3 [$C(CH_3)_3$], 38.2 ($CH_2C_6H_4O$), 45.6 (CH_2NH), 52.0 (CHNH), 70.1 ($OCH_2C_6H_5$), 80.1 [$C(CH_3)_3$], 115.2, 121.9, 125.0, 127.4, 128.0, 128.6, 129.1, 130.2, 137.0, 144.8, 153.6, 157.9 ($CH_2C_6H_4O$, $OCH_2C_6H_5$, *p*-$C_6H_4NO_2$), 156.0 [*C*(O)]. FAB MS: *m/z* = 522.2 $[M + H]^+$. – $C_{28}H_{31}N_3O_6$ (521.57) calcd. C 64.48, H 5.99, N 8.06; found C 64.53, H 5.97, N 8.05.

c) Activated Leucine Monomer : 1.9 g (4.9 mmol, 89%) white solid was obtained from **3c** (1.3 g, 6.12 mmol); m.p. > 110 °C (decomp.). R_f (2:1 hexanes:EtOAc): 0.47. – $[\alpha]_D^{23}$ = – 34.0 (c = 0.51, dioxane). – ^1H NMR ($CDCl_3$): δ = 0.94 [m, 6 H, $CH(CH_3)_2$], 1.25–1.80 [bm, 3 H, $CH(CH_3)_2$ + $CH_2CH(CH_3)_2$], 1.44 [s,9 H, $C(CH_3)_3$],

3.16–3.40 (m, 2 H, C*H*$_2$NH), 3.84 (bs, 1 H, C*H*NH), 4.52 (d, *J* = 7.7 Hz, 1 H, CHN*H*), 5.96 [bs, 1 H, N*H*C(O)O*p*-$C_6H_4NO_2$], 7.27–7.33 (m, 2 H, 2 × *p*-$C_6H_4NO_2$), 8.20–8.25 (m, 2 H, 2 × *p*-$C_6H_4NO_2$). – ^{13}C NMR ($CDCl_3$): δ = 22.0 [CH(CH_3)$_2$], 23.0 [1 × CH(CH_3)$_2$], 24.8 [1 × CH(CH_3)$_2$], 28.4 [C(CH_3)$_3$], 41.9 [CH_2CH(CH_3)$_2$], 47.2 (CH_2NH), 49.0 (CHNH), 79.9 [*C*(CH_3)$_3$], 121.9, 125.1, 144.7, 153.6 (*p*-$C_6H_4NO_2$), 156.1 [*C*(O)], 156.6 [*C*(O)]. FAB MS: *m/z* = 382.2 [M + H]$^+$. – $C_{18}H_{27}N_3O_6$ (381.43) calcd. C 56.68, H 7.13, N 11.02; found C 56.25, H 7.01, N 10.89.

d) Activated Serine Monomer: 0.65 g (1.60 mmol, 64%) white solid was obtained from **3d** (0.69 g, 2.5 mmol); m.p. > 120 °C (decomp.). R_f (2:1 hexanes:EtOAc): 0.48. – $[\alpha]^{23}_D$ = + 2.1 (c = 0.53, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.45 [s,9 H, C(C*H*$_3$)$_3$], 3.44–3.61 (m, 4 H, CHC*H*$_2$O + C*H*$_2$NH), 3.97 (m, 1 H, C*H*NH), 4.54 (d, *J* = 1.8 Hz, 2 H, C*H*$_2$$C_6H_5$), 5.11 (d, *J* = 8.0 Hz, 1 H, CHN*H*), 5.88 (s, 1 H, CH_2N*H*), 7.26–7.39 (m, 7 H, C_6*H*$_5$ + 2 × *p*-$C_6H_4NO_2$), 8.20–8.25 (m, 2 H, 2 × *p*-$C_6H_4NO_2$). – ^{13}C NMR ($CDCl_3$): δ = 28.2 [C(CH_3)$_3$], 44.1 (CHCH_2O), 50.0 (CHNH), 70.3 (O$CH_2C_6H_5$), 73.5 (CH_2NH), 80.0 [*C*(CH_3)$_3$], 121.9, 125.1, 127.8, 128.0, 128.6, 137.5, 144.8, 153.7 (*C*$_6H_5$, *p*-$C_6H_4NO_2$), 156.1 [*C*(O)]. FAB MS: *m/z* = 446.2 [M + H]$^+$. – $C_{22}H_{27}N_3O_7$ (445.47) calcd. C 59.32, H 6.11, N 9.43; found C 59.17, H 6.23, N 9.09.

e) Activated Lysine Monomer: 1.1 g (2.0 mmol, 98% over two steps) white solid was obtained from 3e (0.75 g, 2.1 mmol); m.p. > 103 °C (decomp.). R_f (1:1 hexanes:EtOAc): 0.46. – $[\alpha]^{23}_D$ = – 17.6 (c = 0.52, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.44 [s,9 H, C(C*H*$_3$)$_3$], 3.18–3.40 [m, 4 H, CHC*H*$_2$(CH_2)$_3$ + C*H*$_2$NH], 3.74 (m, 1 H, C*H*NH), 4.74 (d, 1 H, *J* = 8.0 Hz, NH), 4.86 (s, 1 H, NH), 5.10 (s, 1 H, C*H*$_2$$C_6H_5$), 5.95 (s, 1 H, CH_2N*H*), 7.26–7.36 (m, 7 H, C_6*H*$_5$ + 2 × *p*-$C_6H_4NO_2$), 8.20–8.24 (m, 2 H, 2 × *p*-$C_6H_4NO_2$). – ^{13}C NMR ($CDCl_3$): δ = 28.3 [C(CH_3)$_3$], 44.2 (CHCH_2O), 50.1 (CHNH), 70.3 (O$CH_2C_6H_5$), 73.6 (CH_2NH), 80.2 [*C*(CH_3)$_3$], 115.6, 121.9, 125.1, 127.7, 128.6, 137.4, 144.8 (C_6H_5, *p*-$C_6H_4NO_2$), 153.6 [*C*(O)], 155.6 [*C*(O)]. FAB MS: *m/z* = 531.2 [M + H]$^+$. – $C_{26}H_{34}N_4O_8$ (530.58) calcd. C 58.86, H 6.46, N 10.56; found C 58.17, H 6.45, N 10.28.

f) Activated Glycine Monomer: The product precipitated during the synthesis. 1.3 g (4.0 mmol, 78%) white solid was obtained from 4f (Scheme 1) wherein R is hydrogen (0.81 g, 5.1 mmol); m.p. > 133 °C (decomp.) R_f (1:1 hexanes:EtOAc): 0.48. – ^{1}H NMR (D_6[DMSO]): δ = 1.38 [s,9 H, $C(CH_3)_3$], 3.00–3.20 [m, 4 H, $CH_2NHC(O)Op$-$C_6H_4NO_2$ + $BocNHCH_2$], 6.87 (m, 1 H, *NH*Boc) 7.37–7.41 (m, 2 H, 2 × p-$C_6H_4NO_2$), 8.00 (m, 1 H, $NHC(O)Op$-$C_6H_4NO_2$], 8.23–8.27 (2 × p-$C_6H_4NO_2$). – ^{13}C NMR (D_6[DMSO]): δ = 28.2 [$C(CH_3)_3$], 77.7 [$C(CH_3)_3$], 122.3, 125.1, 144.8, 153.1 (p-$C_6H_4NO_2$), 155.6 [*C*(O)], 156.3 [*C*(O)]. FAB MS: *m/z* = 326.1 [M + H]$^+$. – $C_{14}H_{19}N_3O_6$ (325.13) calcd. C 51.69, H 5.89, N 12.92; found C 51.25, H 5.76, N 12.62.

Example 2: Preparation of starting compound (4) as used in Example 1

a) Amino Acid Amides 2 of Scheme 1, General Procedure: A solution of Boc-protected amino acid 1 (10.0 mmol) and TEA (1.55 mL, 11.0 mmol) in THF (6 mL) was cooled to –15 °C (ice–salt bath) under a nitrogen atmosphere. A solution of ethyl chloroformate (1.05 mL, 11.0 mmol) in THF (10 mL) was added dropwise. After stirring for 25 min at –15 °C, a 25% solution of NH_3 in water (3.75 mL) was added in one portion and stirring was continued for 3 h at 0–5 °C. The volatiles were evaporated in vacuo and the pH was adjusted to 2–3 with 1 N $KHSO_4$. The aqueous layer was extracted with EtOAc (2 ×) and the combined organic layers were washed with 1 N $NaHCO_3$ (3 ×), water (1 ×) and brine, and dried (Na_2SO_4). The solvent was removed in vacuo to give the Boc-protected amino acid amide.

i) Phenylalanine Amide 2a: Yield 2.52 g (9.5 mmol, 95%) white solid; m.p. 144-145 °C. R_f (EtOAc): 0.66. – $[\alpha]_D^{24}$ = + 1.26 (c = 1.02, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.40 [s, 9 H, $C(CH_3)_3$], 3.06 (d, J = 4.1 Hz, 2 H, $CH_2C_6H_5$), 4.39 (m, 1 H, *CH*NH), 5.14 (d, J = 8.1 Hz, 1 H, NH), 5.68 and 5.96 (bs, 2 H, NH_2), 7.22–7.33 (m, 5 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 28.2 [$C(CH_3)_3$], 38.5 ($CH_2C_6H_5$), 55.5 (CHNH), 80.2 [$C(CH_3)_3$], 126.9, 128.6, 129.3, 136.7, 157.9 (C_6H_5), 155.4 [$C(O)OC(CH_3)_3$], 173.9 [$C(O)NH_2$]. – FAB MS: *m/z* = 265.2 [M + H]$^+$.

ii) Tyosine Amide 2b: Yield 3.65 g (9.9 mmol, 99%) white solid; m.p.171-172 °C. R_f (EtOAc): 0.68. – $[\alpha]_D^{24}$ = + 4.59 (c = 0.76, dioxane).– ^{1}H NMR ($CDCl_3$): δ = 1.41 [s, 9 H, C(CH_3)$_3$], 3.00 (d, J = 5.9 Hz, 2 H, CH_2Ar), 4.32 (m, 1 H, *CH*NH), 5.03 (s, 2 H, benzyl CH_2), 5.08 (bs, 1 H, NH), 5.60 and 5.88 (bs, 2 H, NH_2), 6.91 (d, J = 8.4 Hz, 2 H, $CH_2C_6H_4O$), 6.91 (d, J = 8.1 Hz, 2 H, $CH_2C_6H_4O$), 7.26–7.48 (m, 9 H, $OCH_2C_6H_5$). – ^{13}C NMR ($CDCl_3$): δ = 28.3 [C(CH_3)$_3$], 37.6 ($CHCH_2C_6H_4O$), 55.7 (CHNH), 70.1 ($OCH_2C_6H_5$), 80.3 [*C*(CH_3)$_3$], 115.2, 127.4, 128.0, 128.6, 128.9, 129.3, 130.4, 137.0 ($CH_2C_6H_4O$, $OCH_2C_6H_5$), 155.4 [*C*(O)OC(CH_3)$_3$], 174.0 [*C*(O)NH_2]. FAB MS: m/z = 371.2 $[M + H]^+$.

iii) Leucine Amide 2c: Yield 2.23 g (9.7 mmol, 97%) white solid; m.p. 137-138 °C. R_f (EtOAc): 0.64. – $[\alpha]_D^{24}$ = – 32.7 (c = 1.01, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 0.93 [m, 6 H, CH(CH_3)$_2$], 1.43 [s, 9 H, C(CH_3)$_3$], 1.43–1.80 [m, 3 H, *CH*(CH_3)$_2$ + CH_2CH(CH_3)$_2$], 4.16 (m, 1 H, *CH*NH), 5.03 (bd, 1 H, CHN*H*), 5.83 and 6.37 (bs, 2 H, NH_2). – ^{13}C NMR ($CDCl_3$): δ = 21.9 [CH(CH_3)$_2$], 22.9 [1 × CH(CH_3)$_2$], 24.7 [1 × CH(CH_3)$_2$], 28.3 [C(CH_3)$_3$], 41.3 [CH_2CH(CH_3)$_2$], 52.6 (CHNH), 80.0 [*C*(CH_3)$_3$], 155.8 [*C*(O)OC(CH_3)$_3$], 175.6 [*C*(O)NH_2]. FAB MS: m/z = 231.2 $[M + H]^+$.

iv) Serine Amide 2d: Yield 2.91 g (9.9 mmol, 99%) white solid; m.p. 96-97 °C. R_f (EtOAc): 0.63. – $[\alpha]_D^{24}$ = + 29.4 (c = 1.01, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.44 [s, 9 H, C(CH_3)$_3$], 3.56–3.89 (bm, 2 H, $CHCH_2O$), 4.31 (m, 1 H, *CH*NH), 4.54 (dd, 2 H, $CH_2C_6H_5$), 5.46 (d, J = 7.4 Hz, 1 H, NH), 6.16 and 6.52 (bs, 2 H, NH_2), 7.27–7.37 (m, 5 H, $CH_2C_6H_5$). – ^{13}C NMR ($CDCl_3$): δ = 28.2 [C(CH_3)$_3$], 53.6 (CHNH), 69.8 ($CHCH_2$), 73.4 ($CH_2C_6H_5$), 80.3 [*C*(CH_3)$_3$], 127.8, 128.0, 128.5, 137.4 ($CH_2C_6H_5$), 155.5 [*C*(O)OC(CH_3)$_3$], 172.3 [*C*(O)NH_2]. FAB MS: m/z = 295.1 $[M + H]^+$.

v) Lysine Amide 2e: Yield 3.49 g (9.2 mmol, 92%) white solid; m.p.137-138 °C. R_f (EtOAc): 0.49. – $[\alpha]_D^{24}$ = – 6.99 (c = 0.99, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, C(CH_3)$_3$], 1.50–1.84 [bm, 6 H, $CHCH_2(CH_2)_3$], 3.19 (bm, 2 H, CHCH_2), 4.11 (m, 1 H, *C*HNH), 5.01 [s, 1 H, $C_6H_5CH_2OC(O)NH$], 5.09 (s, 2 H, $CH_2C_6H_5$), 5.30 (bs, 1 H, CHN*H*), 5.75 and 6.29 (bs, 2 H, NH_2), 7.27–7.36 (m, 5 H, C_6H_5). – ^{13}C NMR ($CDCl_3$): δ = 22.4 (CH_2), 28.3 [C(CH_3)$_3$], 29.4 (CH_2), 31.8 (CH_2), 40.3 (CH_2), 53.8 (CHNH), 66.6 ($CH_2C_6H_5$), 80.0 [*C*(CH_3)$_3$], 128.1, 128.5, 136.6 (C_6H_5), 155.8 [*C*(O)OC(CH_3)$_3$], 156.6 [*C*(O)O$CH_2C_6H_5$], 174.8 [*C*(O)–NH_2]. FAB MS: *m/z* = 380.2 [M + H]$^+$.

b) Amino Acid Nitriles 3 of Scheme 1, General Procedure: Under a nitrogen atmosphere, a solution of amino acid amide **2** (5.0 mmol) in pyridine (6 mL) was cooled to 0 °C (ice bath) and trifluoroacetic anhydride (1.5 mL, 7.3 mmol) was added dropwise. After stirring for 2.5 h, the solvent was removed in vacuo. The residue was dissolved in EtOAc and the organic layer was washed with 1 N $KHSO_4$, water and brine, and dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by column chromatography.

i) Phenylalanine Nitrile 3a: 1.14 g (4.6 mmol, 93%) white solid was obtained from **2a** (1.32 g, 5.0 mmol) after column chromatography (silica, 1.5% MeOH/DCM); m.p. 114-115 °C. R_f (4:1 hexanes:EtOAc): 0.42. – $[\alpha]_D^{25}$ = – 16.4 (c = 0.98, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.44 [s, 9 H, C(CH_3)$_3$], 3.08 (m, 2 H, CH_2Ph), 4.84 (m, 1 H, *C*HNH), 4.94 (d, *J* = 8.7 Hz, 1 H, NH), 7.27–7.40 (m, 5 H, C_6H_5). – ^{13}C NMR ($CDCl_3$): δ = 28.1 [C(CH_3)$_3$], 39.1 ($CH_2C_6H_5$), 43.4 (CHNH), 81.2 [*C*(CH_3)$_3$], 118.3 (CN), 127.7, 128.9, 129.3, 134.0 (C_6H_5), 154.0 [C(O)OC(CH_3)$_3$]. – IR: $\tilde{\nu}$ = 2249 cm^{-1} (CN). – FAB MS: *m/z* = 247.1 [M + H]$^+$.

ii) Tyrosine Nitrile 3b: 3.35 g (9.9 mmol, 99%) white solid was obtained from **2b** (3.55 g, 10,0 mmol) after column chromatography (silica, 1% MeOH/DCM); m.p. 126-127 °C. R_f (4:1 hexanes:EtOAc): 0.33. – $[\alpha]_D^{25}$ = – 4.62 (c = 1.03, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.45 [s,9 H, C(CH_3)$_3$], 3.03 (m, 2 H, CHCH_2Ph), 4.79 (m, 1 H,

CHNH), 5.07 (s, 2 H, $OCH_2C_6H_5$), 6.98 (d, J = 8.8 Hz, 2 H, $CH_2C_6H_4O$), 7.21 (d, J = 8.8 Hz, 2 H, $CH_2C_6H_4O$), 7.34–7.46 (m, 5 H, $OCH_2C_6H_5$). – ^{13}C NMR ($CDCl_3$): δ = 28.2 [$C(CH_3)_3$], 38.4 ($CHCH_2Ph$), 43.7 (CHNH), 70.1 (OCH_2Ph), 81.3 [$C(CH_3)_3$], 118.4 (CN), 115.4, 126.2, 127.4, 128.0, 128.6, 130.6, 136.9 ($CH_2C_6H_4O$, $OCH_2C_6H_5$), 158.6 [$C(O)OC(CH_3)_3$]. – IR: $\tilde{\nu}$ = 2250 cm^{-1} (CN). – FAB MS: m/z = 353.2 $[M + H]^+$.

iii) Leucine Nitrile 3c: 2.23 g (8.9 mmol, 89%) white solid was obtained from **2c** (2.31 g, 10.0 mmol) after column chromatography (silica, 1% MeOH/DCM); m.p. 46-47 °C. R_f (4:1 hexanes:EtOAc): 0.53. – $[\alpha]_D^{25}$ = – 58.9 (c = 0.98, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 0.98 [d, 6 H, $CH(CH_3)_2$], 1.47 [s,9 H, $C(CH_3)_3$], 1.58–1.89 [bm, 3 H, $CH(CH_3)_2$ + $CH_2CH(CH_3)_2$], 4.60 (m, 1 H, CHNH), 4.74 (d, J = 8.1 Hz, 1 H, CHNH). – ^{13}C NMR ($CDCl_3$): δ = 21.8 [$CH(CH_3)_2$], 22.1 [1 × $CH(CH_3)_2$], 24.7 [1 × $CH(CH_3)_2$], 28.2 [$C(CH_3)_3$], 40.9 [$CH_2CH(CH_3)_2$], 42.0 (CHNH), 81.0 [$C(CH_3)_3$], 119.1 (CN), 154.2 [$C(O)OC(CH_3)_3$]. – IR: $\tilde{\nu}$ = 2243 cm^{-1} (CN). – FAB MS: m/z = 213.2 $[M + H]^+$.

iv) Serine Nitrile 3d: 2.20 g (8.0 mmol, 83%) white solid was obtained from **2d** (2.82 g, 9.6 mmol) after column chromatography (silica, 0.25% MeOH/DCM); m.p. 62-63 °C. R_f (4:1 hexanes:EtOAc): 0.60. – $[\alpha]_D^{25}$ = – 9.28 (c = 1.03, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.47 [s, 9 H, $C(CH_3)_3$], 3.62–3.74 (bm, 2 H, $CHCH_2O$), 4.62 (s, 2 H, $CH_2C_6H_5$), 4.73 (m, 1 H, CHNH), 5.36 (bd, 1 H, NH), 7.27–7.37 (m, 5 H, C_6H_5). – ^{13}C NMR ($CDCl_3$): δ = 28.1 [$C(CH_3)_3$], 42.5 (CHNH), 68.9 ($CHCH_2$) 73.5 ($CH_2C_6H_5$), 81.1 [$C(CH_3)_3$], 117.5 (CN), 127.8, 128.1, 128.5, 136.7 (C_6H_5), 154.2 [$C(O)OC(CH_3)_3$]. – IR: $\tilde{\nu}$ = 2247 cm^{-1} (CN). – FAB MS: m/z = 277.1 $[M + H]^+$.

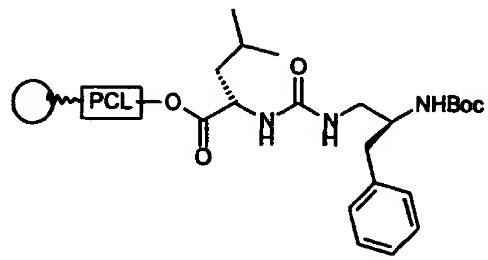
v) Lysine Nitrile 3e: 0.87 g (2.4 mmol, 96%) white solid was obtained from **2e** (0.95 g, 2.5 mmol) after column chromatography (silica, 0.5% MeOH/DCM); m.p. 108-110 °C. R_f (2:1 hexanes:EtOAc): 0.43. ^{1}H. – $[\alpha]_D^{25}$ = – 25.0 (c = 0.99, dioxane). – NMR ($CDCl_3$): δ = 1.45 [s,9 H, $C(CH_3)_3$], 1.45–1.81 [bm, 6 H, $CHCH_2(CH_2)_3$], 3.20 (bm, 2 H, $CHCH_2$), 4.49 (m, 1 H, CHNH), 5.03 [s, 1 H,

$C_6H_5CH_2OC(O)N$*H*], 5.09 (s, 2 H, C*H*$_2C_6H_5$), 5.28 (bd, 1 H, CHN*H*), 7.27–7.35 (m, 5 H, C_6*H*$_5$). – ^{13}C NMR ($CDCl_3$): δ = 22.1 (CH_2), 28.0 [C(C*H*$_3$)$_3$], 28.9 (CH_2), 32.2 (CH_2), 40.0 (CH_2), 42.0 (CHNH), 66.4 ($CH_2C_6H_5$), 80.7 [*C*(CH_3)$_3$], 118.8 (CN), 127.8, 127.8, 128.3, 136.4 (*C*$_6H_5$), 154.4 [*C*(O)OC(CH_3)$_3$], 156.5 [*C*(O)O$CH_2C_6H_5$]. – IR: $\tilde{\nu}$ = 2244 cm^{-1} (CN). – FAB MS: *m/z* = 362.2 [M + H]$^+$.

vi) *N*-Boc-Ethylenediamine 4f: A solution of di-*tert*-butyl dicarbonate (21.8 g, 100 mmol) in dioxane (330 mL) was added dropwise to a solution of ethylenediamine (46.7 mL, 700 mmol) in dioxane (330 mL) over a period of 5 h. After evaporation of the solvent, water (450 mL) was added to the residue, and the insoluble *bis*-substituted product was removed by filtration. The aqueous layer was extracted with DCM (3 × 200 mL), and the combined organic layers were washed with brine and dried (Na_2SO_4). After evaporation of the solvent, the product was obtained as a slightly yellow oil (14.2 g, 89 mmol, 89% based on di-*tert*-butyl dicarbonate). – ^{1}H NMR ($CDCl_3$): δ = 1.33 [s,9 H, C(C*H*$_3$)$_3$], 1.44 (s, 2 H, NH_2), 2.67 (t, *J* = 5.9 Hz, 2 H, C*H*$_2$NH), 3.07 (q, *J* = 5.9 Hz, 2 H, NH_2C*H*$_2$), 5.23 (bs, 1 H, CH_2N*H*). – ^{13}C NMR ($CDCl_3$): δ = 28.2 [C(C*H*$_3$)$_3$], 41.6 (CH_2NH_2), 66.8 (CH_2NHBoc), 79.0 [*C*(CH_3)$_3$], 156.1 [C(O)OC(CH_3)$_3$].

Example 3: Preparation of oligourea peptidomimetics

a) Coupling of Resin with Fmoc-Leu-OH, General Procedure: Photolinker resin 5 (0.23 mmol/g) was coupled with Fmoc-Leu-OH using the procedure of Sieber (Tetrahedron Lett. (1987), 28, 6147-6150). The loading was determined by Fmoc cleavage from a resin sample, and was generally 0.20 mmol/g. The resin was treated for 15 min with 5 mL of a capping solution (a solution of acetic anhydride (0.5 M), DiPEA (0.125 M), HOBt (0.015 M) and a catalytic amount of DMAP in NMP) per g resin to acetylate the remaining hydroxyl functions. Agitation was effected by nitrogen bubbling. The resin was filtered, washed with NMP (3 ×) and DCM (3 ×), and dried.



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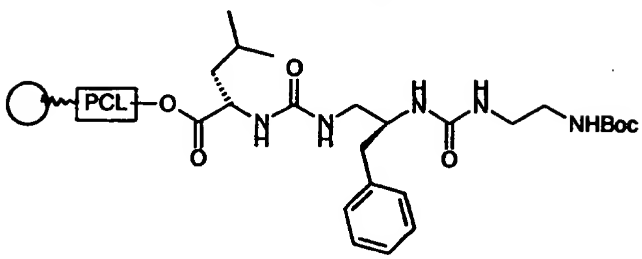

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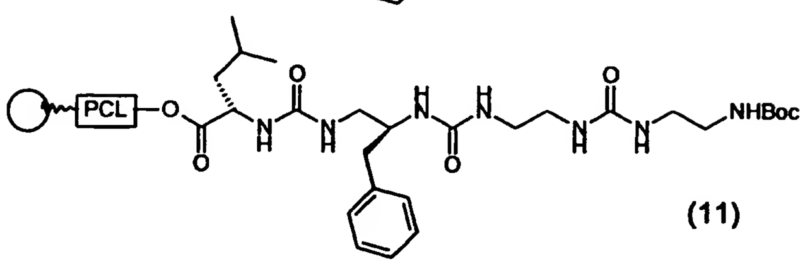

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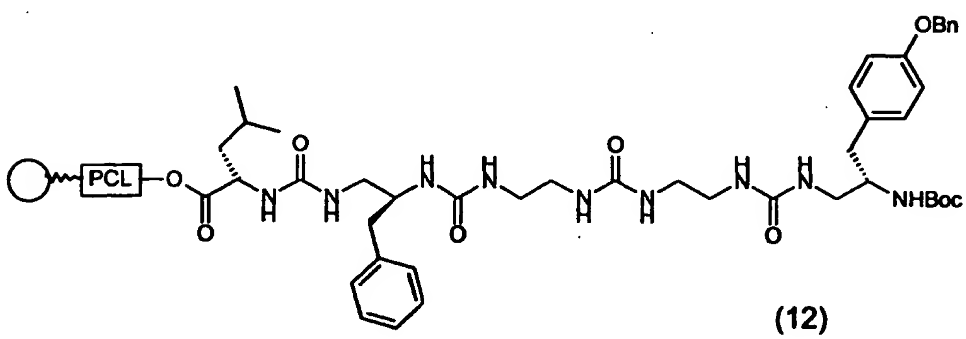
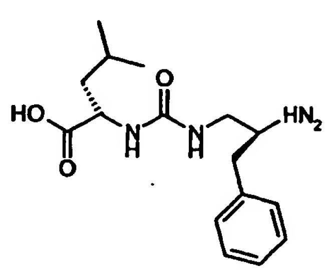


(12)

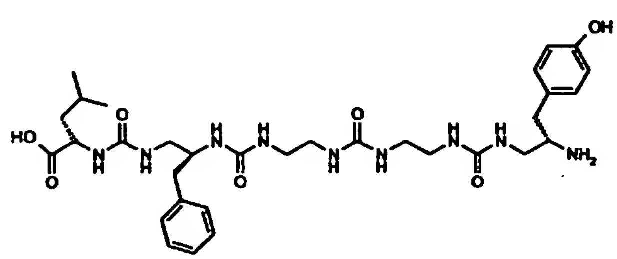
Preparation of Resin-Bound Urea Derivatives Of YGGFL 9-12, General Procedure: Photolinker resin **5** esterified with Fmoc-Leu-OH (1 g, 0.20 mmol/g), was washed with NMP (3 ×) and treated with a solution of 20% piperidine in NMP (5 mL). After 20 min the solvent was removed by filtration and the resin was washed with NMP (5 ×), giving product (6) wherein R^1 is $CH_2CH(CH_3)_2$. Subsequently, a solution of activated phenylalanine monomer of Example 1 a) (3 equivs) and DiPEA (3.5 equivs) in NMP (5 ml) was added. After 3 h, the solution was drained and the resin was washed with NMP (3 ×) and DCM (3 ×). Synthesis

of resin-bound dimer **9** was now complete. For synthesis of trimer **10**, the Boc-groups were removed by treatment with a 1:1 TFA:DCM mixture (10 mL) for 30 min. The resin was washed with DCM (3 ×), 10% TEA/DCM (3 ×), DCM (3 ×) and NMP (3 ×), and subjected to a coupling cycle with activated glycine monomer of Example 1 f). Resin-bound tetramer **11** and pentamer **12** were prepared by similar deprotection and coupling cycles with subsequently activated glycine monomer of Example 1 f) and tyrosine monomer of Example 1 b) resp.

Urea Dimer 13: To resin **9** (250 mg, 0.19 mmol/g), THF (10 mL) was added. The reaction vessel was evacuated and filled with Argon (3×), and suspended above the UV lamp in a shaking device. The set up was covered with aluminium foil and irradiated for 24 h, under continuous shaking. Samples were taken after 10 min, 1, 2, 3, 4, 5, 6, 7, 8, 22, 23 and 24 h, and analyzed by HPLC. Cleavage was complete after 24 h. The resin was filtrated and washed with THF (3 ×). The filtrate was evaporated. This yielded 21.1 mg (>100%) of the crude product. The Boc group in 11 mg of the crude product was removed directly (13) with 30% TFA/DCM at 0 °C, and the product was purified by preparative HPLC. The pure product **13** was obtained after lyophilisation as a white solid (6.1 mg, 0.0199 mmol, 80%). – ^{1}H NMR (D_6[DMSO]): δ = 0.84 [m, 6 H, $CH(CH_3)_2$], 1.15–1.50 [m, 2 H, $CH_2CH(CH_3)_2$], 1.58–1.74 [m, 1 H, $CH(CH_3)_2$], 2.45–2.49 (m, 2 H, $CH_2C_6H_5$), 2.75–2.85 (m, 2 H, NCH_2CH), 3.17 (m, 1 H, $CHCH_2C_6H_5$), 4.10 (m, 1 H, $CHCOOH$), 6.32 (m, 2 H, N*H*), 6.43(d, *J* = 8.4 Hz, 1 H, NH), 7.24–7.36 (m, 5 H, C_6H_5). – ^{13}C NMR (D_6[DMSO]): δ = 21.6 [$CH(CH_3)_2$, 2×, diast.], 22.7 [1 × $CH(CH_3)_2$], 24.2 [1 × $CH(CH_3)_2$], 37.5, 37.6 (CH_2, 2×, diast.) 40.6 (CH_2), 42.1, 42.4 (CH_2, 2×, diast.), 49.6, 49.9 (NCH_2CH, 2×, diast.), 54.6, 54.7 (ring *C*H, 2×, diast.), 77.4 [$C(CH_3)_3$], 126.1, 128.2, 129.1, 138.7 (C_6H_5), 155.4 [$C(O)OC(CH_3)_3$, 2×, diast.], 156.9, 157.0 [ring *C*(O), 2×, diast.], 174.9 [ring *C*(O), 2×, diast.]. FAB MS: *m/z* = 390.2 $[M+H]^+$. HPLC: >99% pure.



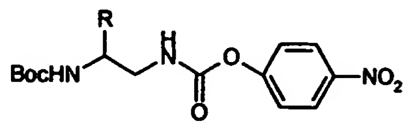
Urea Pentamer 14: To resin **12** (500 mg, 0.20 mmol/g), THF (10 mL) was added. The reaction vessel was evacuated and filled with Argon (3 ×), and suspended above the UV lamp in a shaking device. The set up was covered with aluminium foil and irradiated for 24 h, under continuous shaking. After 24 h, the resin was filtrated and washed with THF (3 ×), and the filtrate was evaporated. The benzyl group in the tyrosine side chain of the crude product was removed by catalytic hydrogenation with 5% Pd/C. Preparative HPLC and subsequential lyophilisation gave the pure product **14** as a white solid (27 mg, 0.040 mmol, 40%). – ^{1}H NMR (D_6[DMSO]): δ = 0.85 [m, 6 H, CH(CH_3)$_2$], 1.20–1.50 [m, 2 H, CH_2CH(CH_3)$_2$], 1.65–1.78 [m, 1 H, CH(CH_3)$_2$], 2.45–2.75 (m, 2 H, CH$CH_2C_6H_5$ + $CH_2C_6H_4$O), 2.83–3.05 (m, 10 H, 2 × CH_2CH_2 + CH_2CHNHBoc), 3.25–3.38 (m, 2 H, NCH_2CH$CH_2C_6H_5$), 3.42–3.58 (m, 1 H, $CH$$CH_2C_6H_4$O), 3.84–3.98 (m, 1 H, N$CH_2$$CH$$CH_2C_6H_5$), 4.03–4.18 (m, 1 H, ring CH), 4.51 (s, 1 H, NH), 5.03 (s, 2 H, benzyl CH_2), 5.65–6.10 (m, 5 H, urea NH), 6.60–6.70 (m, 1 H, NH), 6.88 (d, J = 8.4 Hz, 2 H, C_6H_4O), 7.07 (d, J = 8.4 Hz, 2 H, C_6H_4O), 7.13–7.42 (m, 5 H, $CHCH_2C_6H_5$ + C_6H_4O), 8.22 (d, J = 4.3 Hz, 1 H, NH). – ^{13}C NMR (D_6[DMSO]): δ = 21.5 [CH(CH_3)$_2$], 22.8 [1 × CH(CH_3)$_2$], 24.2 [1 × CH(CH_3)$_2$], 35.2 (CH_2), 38.4 (CH_2), 38.7 (CH_2), 40.6 (CH_2), 41.1 (CH_2), 42.8 (CH_2), 50.9 (CH), 51.6 (CH), 53.4 (CH), 115.5, 126.1, 128.2, 129.3, 130.3 (Ar CH), 126.3, 139.0, 156.5 (quat. C Ar), 156.9 158.2, 158.7, 159.1, 175.5 [C(O)]. FAB MS: m/z = 672.4 [M + H]$^+$. HPLC: >90% pure.



(14)

Claims:

1. Boc-protected monomers of the formula



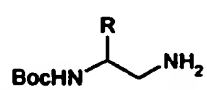
(I)

wherein R represents a side-chain of a natural or unnatural, common or uncommon amino acid, wherein optionally present functional groups are protected.

2. Boc-protected monomers as claimed in claim 1 wherein R represents a side-chain of a natural or unnatural amino acid.

3. Boc-protected monomers as claimed in claim 2 wherein R represents the side-chain of phenylalanine, O-protected tyrosine, leucine, O-protected serine, NH-protected lysine or glycine.

4. Process for the preparation of monomers as claimed in claims 1-3, characterized in that a compound of the formula



(II)

is reacted with 4-nitrophenyl chloroformate under basic conditions, to give an monomer of the formula (I), wherein R has the meaning given in claim 1.

5. Use of monomers as claimed in claims 1-3 for the solid phase synthesis of oligourea peptidomimetics having a free carboxyl terminus, characterized in that a) an N-protected amino acid is coupled to a photocleavable linker (PCL) containing resin, b) the protective group is removed, c) a solution of an activated monomer as claimed in claims 1-3 is added, d) the protecting group is removed from the N-terminus, and e) steps c) and d) are repeated n-times depending on the length of the desired oligourea peptidomimetic, wherein n is

the number of monomers, and f) the oligourea peptidomimetic is cleaved from the resin, and the side-chain(s) protecting group(s) and/or the N-protecting Boc-group are removed.

INTERNATIONAL SEARCH REPORT

Intc onal Application No
PCT/EP 00/03735

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C271/52 C07C269/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KRUIJTZER J A W ET AL: "Approaches to the Synthesis of Ureapeptoid Peptidomimetics" TETRAHEDRON LETTERS, vol. 38, no. 30, 28 July 1997 (1997-07-28), page 5335-5338 XP004083313 ISSN: 0040-4039 the whole document	1-5
A	WILSON M E ET AL: "An Efficient Synthesis of N,N'-Linked Oligoureas" TETRAHEDRON LETTERS, vol. 39, no. 37, 10 September 1998 (1998-09-10), page 6613-6616 XP004132559 ISSN: 0040-4039 the whole document	1-5

-/--

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 July 2000	04/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rufet, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KEVIN BURGESS ET AL.: "Solid phase syntheses of Oligoureas" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 119, no. 7, 19 February 1997 (1997-02-19), pages 1556-1564, XP002115550 DC US cited in the application the whole document	1-5

1

NR

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

Date of mailing (day/month/year) 04 December 2000 (04.12.00)	
International application No. PCT/US00/01957	**Applicant's or agent's file reference** UMDNJ RWJ 99-02
International filing date (day/month/year) 25 January 2000 (25.01.00)	**Priority date** (day/month/year) 25 January 1999 (25.01.99)
Applicant RANA, Tariq, M.	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   23 August 2000 (23.08.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Pascal Piriou Telephone No.: (41-22) 338.83.38

4

PATENT COOPERATION TREATY

PCT

REC'D 23 APR 2002

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

9/889982 (0120)

Applicant's or agent's file reference UMDNJ RWJ 99	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/01957	International filing date *(day/month/year)* 25 JANUARY 2000	Priority date *(day/month/year)* 25 JANUARY 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 23 AUGUST 2000	Date of completion of this report 22 MARCH 2002
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer J. S. Parkin Telephone No. (703) 308-1234

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description.
pages 1-15 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the claims
pages 16-18 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the drawings:
pages 1-4 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the sequence listing part of the description.
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language ______ which is.

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form

[ ] furnished subsequently to this Authority in computer readable form

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of.

[X] the description, pages NONE

[X] the claims, Nos NONE

[X] the drawings sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)) **

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/01957

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 25

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination *(specify)*.

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 25 are so unclear that no meaningful opinion could be formed *(specify)*.

the claim is an improper multiple dependent claim and fails to comply with PCT Rule 6.4(a).

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/01957

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-5, 7-12, and 15-24	YES
	Claims	6, 13, 14, and 26	NO
Inventive Step (IS)	Claims	1-5, 7-12, 15-23	YES
	Claims	6, 13, 14, 24, and 26	NO
Industrial Applicability (IA)	Claims	1-24 and 26	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-5, 7-12, and 15-23 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed oligourea Tat derivative and associated methods of use.

Claims 6, 13, 14, and 26 lack novelty under PCT Article 33(2) as being anticipated by Mark *et al.* (1988). This teaching discloses compounds having the same structure claimed by applicants (i.e., compare Figure 1B from the instant application with the compound set forth on p. 217 of the cited reference). Since the compounds of the prior art share the same basic structural features, it is also reasonable to conclude that they will share the same nucleic acid binding activities since this is an inherent property of polyurea, absent evidence to the contrary.

Claim 24 lacks an inventive step under PCT Article 33(3) as being obvious over Mark *et al.* (1998). As set forth supra, Mark and colleagues provide oligoureas with high and specific binding activities for nucleic acids. It would have been *prima facie* obvious to one of ordinary skill in the art to prepare kits comprising these oligoureas since this would facilitate the rapid and facile use of these compounds in routine procedures, including diagnostic assays.

Claims 1-24 and 26 meet the criteria set out under PCT Article 33(4).

——— NEW CITATIONS ———

NONE

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): A01N 47/28; A61K 31/17, 31/00; C12Q 1/68, 1/58 and US Cl.: 514/2, 588; 435/6, 12; 422/61

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/01957

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A01N 47/28; A61K 31/17, 31/00; C12Q 1/68, 1/58 US CL :514/2, 588; 435/6, 12; 422/61 According to International Patent Classification (IPC) or to both national classification and IPC
B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/2, 588; 435/6, 12; 422/61
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) USPATFUL, CABA, AIDSLINE, MEDLINE, WPIDS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,843,995 A (RANA et al.) 01 December 1998, see entire document.	1-24 and 26
X ----- Y	MARK, H.F., et al., eds. Encyclopedia of Polymer Science and Engineering. John Wiley & Sons, Inc. New York. 1988. Vol. 13. pages 212-243, see entire document.	6, 13, 14, 26 ---------- 24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 MAY 2000	04 AUG 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Jeffrey S. Parkin, Ph.D. Telephone No. (703) 308-1234

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/01957

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [X] Claims Nos.: 25
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
[ ] The additional search fees were accompanied by the applicant's protest.
[ ] No protest accompanied the payment of additional search fees.